Comparison of Survival Prediction with Single versus Combination Use of Microcirculation End Point Resuscitation in Sepsis and Septic Shock

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ABSTRAK

Latar belakang: *bersihan laktat dan saturasi oksigen vena sentral ($ScvO_2$) adalah dua metode untuk menentukan kecukupan oksigenasi jaringan. Di antara kedua metode tersebut, terdapat kontroversi metode yang lebih berhubungan dengan dan dapat memprediksi mortalitas pasien sepsis dan renjatan sepsis. Penelitian ini bertujuan untuk menilai hubungan pencapaian target parameter akhir resusitasi mikrosirkulasi dan mortalitas dini pasien sepsis dan renjatan sepsis.* ***Metode:*** *penelitian ini merupakan studi kohort pada pasien sepsis dan renjatan sepsis dewasa di Unit Perawatan Intensif RS Cipto Mangunkusumo, Indonesia. Data parameter akhir resusitasi dan luaran pasien diamati dalam 120 jam pertama perawatan. Analisis Cox's proportional hazard regression digunakan untuk menilai risiko mortalitas dini pada kelompok subjek yang mencapai target bersihan laktat saja, target $ScvO_2$ saja, kedua target dan tidak mencapai target apapun dalam 6 jam pertama sesudah awitan resusitasi, dengan penyesuaian terhadap jumlah disfungsi organ.* ***Hasil:*** *subjek terdiri atas 268 pasien. Terdapat perbedaan risiko mortalitas yang bermakna antara kelompok subjek yang mencapai kedua target dibandingkan kelompok subjek yang mencapai target $ScvO_2$ saja (adjusted hazard ratio [aHR] 13,47; 95% interval kepercayaan [IK] 5,17-35,08) dan yang tidak mencapai target apapun (aHR 16,12; 95% CI 7,43-34,95). Tidak terdapat perbedaan risiko mortalitas yang bermakna antara kelompok subjek yang mencapai kedua target dibandingkan kelompok subjek yang mencapai target laktat saja (aHR 2,29; 95%CI 0,83-6,32).* ***Kesimpulan:*** *pada pasien sepsis dan renjatan sepsis, pencapaian target bersihan laktat dan $ScvO_2$ berhubungan dengan risiko mortalitas dini yang tidak berbeda dengan dengan pencapaian target bersihan laktat saja, namun berhubungan dengan peningkatan risiko mortalitas dini dibandingkan dengan pencapaian target bersihan $ScvO_2$ saja.*

Kata kunci: *bersihan laktat, mortalitas dini, renjatan sepsis, saturasi oksigen vena sentral, sepsis.*

ABSTRACT

Background: *lactate clearance and central venous oxygen saturation ($ScvO_2$) are two methods for determining tissue oxygenation adequacy. There is a controversy regarding method better associates with and predicts sepsis and septic shock patients' mortality. This study address the association of achieving one or two targets of microcirculatory resuscitation endpoints and early mortality in sepsis and septic shock.* ***Methods:*** *a cohort study was conducted in adult sepsis and septic shock patients in Intensive Care Unit, Cipto Mangunkusumo Hospital, Indonesia. Patients' resuscitation endpoints data and outcome were observed during the first 120 hours of hospitalization. Cox's proportional hazard regression analysis was used to analyse the early mortality risk in subject groups achieving lactate clearance target only, $ScvO_2$ target only, both targets, and not achieving any target in 6 hours after onset*

of resuscitation adjusted for number of organ dysfunction. ***Results:*** *subjects consisted of 268 patients. There were significant differences in the mortality risk between subjects who achieved both targets with subjects who achieved $ScvO_2$ target only (adjusted hazard ratio [aHR] 13.47; 95% confidence interval [CI] 5.17-35.08) and subjects who not achieve any target (aHR 16.12; 95%CI 7.43-34.95). There were insignificant difference the early mortality risk between subjects who achieved both targets with subjects achieved lactate clearance target only (aHR 2.29; 95%CI 0.83-6.32).* ***Conclusion:*** *in patients with sepsis and septic shock, achievement of lactate clearance and $ScvO_2$ targets associates with similar early mortality risk compared to achievement of lactate clearance target only. However, it associates with lower early mortality risk compared with $ScvO_2$ target only.*

Keywords: *central venous oxygen saturation, early mortality, lactate clearance, septic shock, sepsis.*

INTRODUCTION

New guidelines on sepsis definition by a task force of sepsis expert proposed the presence of acute organ dysfunction in patient with infection as a key determinant of defining sepsis.[1,2] In accordance with this new guidelines, international guidelines for management of sepsis and septic shock in 2016 redefined sepsis-induced hypoperfusion as manifestation of acute organ dysfunction and/or hypotension and increment of serum lactate. In this population, initial resuscitation is strongly recommended.[3] These two new definitions reflect the role of perfusion alteration (i.e. hypoperfusion) as pathophysiology hallmark of septic patient.

Hypoperfusion in sepsis does not only manifest as alteration of macrocirculation hemodynamic parameter (i.e. overt septic shock), but also with alteration of microcirculation hemodynamic parameter (i.e. cryptic septic shock) without alteration of macrocirculation hemodynamic parameter. Microcirculation end points resuscitation have gained many attentions since achievements of microcirculation resuscitation endpoints only could not improve septic patients' survival.[4-7] Lactate clearance >10% and central venous oxygen saturation ($ScvO_2$) >70% are two methods for determining microculation hemodynamic adequacy. Optimal resuscitation should be targeted on both macro- and microcirculation resuscitation endpoints. By achieving these resuscitation endpoints, improvement of organ dysfunction and hence survival can be achieved.[8-12]

Approach on resuscitation using early goal-directed therapy has been challenged by several newer trials, doubting the role of $ScvO_2$ as essential microcirculation resuscitation endpoint.[13-15] In response to these new evidences, Surviving Sepsis Campaign revised the sepsis bundles by eliminating the routine measurement of $ScvO_2$ to be completed within 6 hours of presentation time. Lactate clearance is the only microcirculation endpoint in resuscitation that is recommended to be routinely measured.[3,16] While there is a study revealing a non-inferiority of using lactate clearance compared to $ScvO_2$ as resuscitation endpoint, there is no study comparing survival benefit of achievement of both microcirculation endpoints resuscitation with either one of the microcirculation resuscitation endpoint.[9] This study was aimed to address the association of achieving one or two target of microcirculatory resuscitation endpoints (i.e. lactate clearance >10% and $ScvO_2$ >70%) and early mortality in sepsis and septic shock patients.

METHODS

This was a cohort study using medical record from the Intensive Care Unit of Cipto Mangunkusumo Jakarta, Indonesia in 2013. Intensive Care Unit patients who met the third international consensus definitions for sepsis and septic shock (sepsis-3), aged 18 years and older were included.

Sepsis was defined as an acute change in >2 organ dysfunction caused by infection, while septic shock was defined as persistent hypotension requiring vasopressors to maintain mean arterial pressure (MAP) >65 mmHg and serum lactate >2 mmol/L despite adequate fluid resuscitation in sepsis patients.[1] Subjects' baseline (demographic, clinical) characteristics, macro- and microcirculation resuscitation

endpoints in 6 hours after onset of resuscitation, first 120 hour outcomes and time to outcome were recorded. The endpoints in resuscitation recorded were central venous pressure (CVP), MAP, urine output, hematocrit (Ht), $ScvO_2$, lactate clearance, standard base excess (SBE), and number of organ dysfunction. Lactate clearance was calculated using the formula: [(pre-resuscitation lactate concentration – post-resuscitation lactate concentration) / pre-resuscitation lactate concentration] x 100%.[10] The first 120 hours is the defining time for early mortality in sepsis used in this study, based on definition used on previous sepsis study, Recombinant Human Activated Protein C Worldwide Evaluation in Severe Sepsis.[17]

Subjects were then classified based on resuscitation of microcirculation resuscitation endpoints in 6 hours after onset of resuscitation into four groups, i.e. subject groups achieving lactate clearance >10% only, $ScvO_2$ >70% only, both targets, and not achieving any target.

The sample size of the study was calculated based on an estimated 57% prevalence of subjects who achieved lactate clearance >10% and $ScvO_2$ >70%. Assuming a relative hazard of 1.5, with $\alpha = 0.05$, $\beta = 0.20$ and early mortality prevalence 34%, the required total sample size was calculated to be 268 patients.[18,19]

Cox's proportional hazard regression analysis was used to analyse the risk of early mortality in groups achieving lactate clearance target only, $ScvO_2$ target only, both targets, and not achieving any target in 6 hours after onset of resuscitation. The adjusted hazard ratios were derived from multivariate Cox's proportional hazard models adjusted for number of organ dysfunction, in accordance with conclusion of previous study reported that microcirculation end points of resuscitation and number of organ dysfunction were the predictors for early mortality in severe sepsis and septic shock patients.[20-24] Statistical analyses were performed using the SPSS software version 20.0 (IBM Corp., USA). This study had been approved by the Ethics Committee of The Faculty of Medicine Universitas Indonesia with a reference number 025/H2.F1/ETIK/2013.

RESULTS

A total of 268 sepsis and septic shock patients were enrolled in this study. Subjects had a median age of 49 (interquartile range 25) years old, and 147 (54,9%) were men. The majority of subjects achieved both microcirculation target (51.49%). The characteristics of subjects are presented in **Table 1**. The subject's achievements of endpoints

Table 1. Sepsis and septic shock subjects: comparison based on achievement of microcirculation resuscitation endpoints in 6 hours after onset of resuscitation

Variables	Group achieving LC and $ScvO_2$ target (n=138)	Group achieving LC target only (n=54)	Group achieving $ScvO_2$ target only (n=16)	Group not achieving any target (n=60)
Sex (n, male/female)	72/66	33/21	11/5	31/29
Age (years)[a]	49.5 (26)	48 (26)	51 (21)	50.5 (27)
Septic shock (n, %)	72 (52.2)	24 (44.4)	11 (68.8)	45 (75)
Comorbidity (n, %)				
- Chronic heart failure	18 (13.04)	6 (11.11)	5 (31.25)	11 (18.33)
- Chronic kidney disease, routine dialysis	5 (3.62)	3 (5.56)	1 (6.25)	11 (18.33)
- Cerebrovascular disease	17 (12.32)	8 (14.81)	1 (6.25)	8 (13.33)
- Hepatic cirrhosis	7 (5.07)	0	0	1 (1.67)
- Malignancy	60 (43.48)	14 (25.92)	4 (25)	22(36.67)
- Diabetes mellitus	33 (23.91)	23 (42.59)	4 (25)	21 (35)
Location of infection (n, %)[b]				
- Intracranial	7 (5.07)	2 (3.7)	0	3 (5)
- Respiratory tract	92 (66.67)	36 (6.67)	12 (75)	41 (68.33)
- Intra-abdominal and gastrointestinal tract	41 (29.71)	13 (24.07)	6 (37.5)	24 (40)

Table 1. Sepsis and septic shock subjects: comparison based on achievement of microcirculation resuscitation endpoints in 6 hours after onset of resuscitation (continued)

Variables	Group achieving LC and $ScvO_2$ target (n=138)	Group achieving LC target only (n=54)	Group achieving $ScvO_2$ target only (n=16)	Group not achieving any target (n=60)
- Genito-urinary tract	11 (7.97)	3 (5.56)	1 (6.25)	7 (11.67)
- Skin and soft tissue	20 (14.49)	11 (20.37)	4 (25)	9 (15)
Source of infection (n, %)[b]				
- Community	88 (63.77)	34 (62.96)	14 (87.5)	39 (65)
- Nosocomial	54 (39.13)	23 (42.6)	4 (25)	23 (38.33)
Organ dysfunction based on SOFA (n, %)[b]				
- Respiration	100 (72.5)	44 (81.48)	14 (87.5)	52 (86.7)
- Coagulation	39 (28.26)	14 (25.92)	8 (50)	31 (51.67)
- Cardiovascular	73 (52.9)	23 (42.59)	12 (75)	45 (75)
- Kidney	33 (23.91)	15 (27.78)	5 (31.25)	33 (55)
Number of organ dysfunction based on SOFA (n, %)				
- 1 organ dysfunction	60 (43.47)	23 (42.59)	4 (25)	7 (11.67)
- 2 organ dysfunctions	40 (29)	16 (29.63)	4 (25)	18 (30)
- More than two organ dysfunctions	38 (27.53)	15 (27.78)	8 (50)	35 (58.33)
Early mortality (n, %)	8 (5.79)	7 (12.96)	9 (56.25)	46 (76.67)

[a] data presented as median (interquartile range); [b] subjects fulfill multiple variables were calculated more than once;
Abbreviation: LC: lactate clearance, SOFA: Sequential Organ Failure Assessment

Table 2. Subject's achievements of endpoints in resuscitation within 6 hours after onset of resuscitation

End points resuscitation	Group achieved LC and $ScvO_2$ target (n=138)	Group achieved LC target only (n=54)	Group achieved $ScvO_2$ target only (n=16)	Group not achieved any target (n=60)
Central venous pressure (n, %)				
- 8-12 mmHg	46 (33.34)	15 (27.78)	5 (31.25)	24 (40)
- <8 mmHg	85 (61.59)	36 (66.67)	9 (56.25)	32 (53.33)
- >12 mmHg	7 (5.07)	3 (5.55)	2 (12.5)	4 (6.67)
Mean arterial pressure (n, %)				
- >65 mmHg	124 (89.85)	46 (85.18)	11 (68.75)	45 (75)
- <65 mmHg	14 (10.05)	8 (14.82)	5 (31.25)	15 (25)
Urine output (n, %)				
- >0,5 mL/kg/hour	127 (92.03)	49 (90.74)	11 (68.75)	36 (60)
- <0,5 mL/kg/hour	11(7.97)	5 (9.26)	5 (31.25)	24 (40)
Hematocrit (n, %)				
- >30 %	138 (100)	54 (100)	0	0
- <30%	0	0	16 (100)	60 (100)
Standard base excess (n, %)				
- >-2 mmol/L	66 (47.83)	34 (62.96)	6 (37.5)	15 (25)
- -2 to -5,9 mmol/L	36 (26.09)	7 (12.96)	4 (25)	18 (30)
- -6 to -14,9 mmol/L	32 (23.18)	12 (22.22)	5 (31.25)	22 (36.67)
- <-15 mmol/L	4 (2.9)	1 (1.86)	1 (6.25)	5 (8.33)

in resuscitation are presented in **Table 2**.

Risk of Early Mortality in Subject Groups

Outcome of the subjects are presented in **Table 3**. Cox's proportional hazard regression analysis showed that subjects achieving both targets (lactate clearance and $ScvO_2$) had the lowest risk of early mortality with hazard ratio (HR) 14.99; 95% confidence interval (CI) 5.77-38.9 (p<0.001) compared to subjects who did not achieve $ScvO_2$ target only and HR 23.43; 95%CI 10.98-50.04 (p <0.001) compared with subjects not achieved any target. We found insignificant risk difference between subjects who achieved both targets with subjects who achieved lactate clearance target only (HR 2.32; 95%CI 0.84-6.40, p=0.104).

We adjusted the hazard ratio for number of organ dysfunction and found a significant risk difference between subjects who achieved both targets with subjects who achieved $ScvO_2$ target only (adjusted HR 13.47; 95% CI 5.17-35.08, p<0.001) and subjects who did not achieve any target (adjusted HR 16.12; 95%CI 7.43-34.95, p <0.001). We found insignificant risk difference between subjects who achieved both targets with subjects who achieved lactate clearance target only (adjusted HR 2.29; 95% CI 0.83-6.32, p=0.109) (**Figure 1**).

In sub group analysis of 70 subjects who achieved either lactate clearance or $ScvO_2$ target, failure to achieve lactate clearance target was associated with higher risk of early mortality (adjusted HR 5.92; 95% CI 2.18-16.01).

DISCUSSION

This is the first Indonesian study to assess the association of achieving one or two target of microcirculatory resuscitation endpoints (i.e. lactate clearance and $ScvO_2$) and early mortality in sepsis and septic shock patients. For the

Table 3. Outcome of sepsis and septic shock subjects

Variables	Group achieved LC and $ScvO_2$ target (n=138)	Group achieved LC target only (n=54)	Group achieved $ScvO_2$ target only (n=16)	Group not achieved any target (n=60)
Early mortality (n, %)	8 (5.79)	7 (12.96)	9 (56.25)	46 (76.67)
Mean of survival (hours, 95%CI)	116.1 (112.8-119.3)	113.2 (106.4-120.1)	77.5 (55.4-99.6)	74.1 (64-84.2)

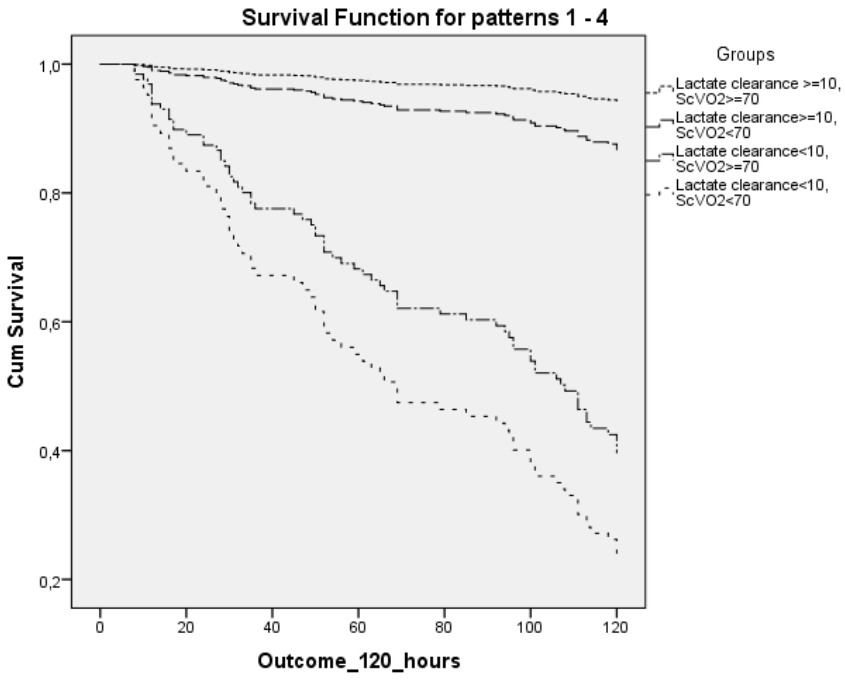

Figure 1. Survival analysis of groups based on targets achievement

determination of cut off period in defining early mortality in this study, we referred to the result of previous study that divided mortality in sepsis patients into 4 periods. Mortality in the first fifth day of sepsis was defined as early mortality. There was different subjects' characteristics and cause of death in the early and late mortality periods. Early mortality was related with number and degree of organ dysfunction, while late mortality was related with number and degree of comorbidities. The differences were also found in the biochemical analysis. In the early mortality group, there was increased level of Interleukin (IL)-6 and decreased circulating leucocyte; while in the late mortality group, there was decreased level of IL-6 and increased level of various inflammatory cytokines, i.e. Macrophage Inflammatory Proteins (MIP)-2, Monocyte Chemoattractant Protein (MCP)-1, IL-1 Receptor Antagonist (IL-1ra), and Soluble Tumor Necrosis Factor Receptor Type I (TNF-SRI), and leucocytes reflecting the role of inflammation as the core pathophysiology of late mortality in sepsis.[17, 25,26]

The basic of organ dysfunction in sepsis is perfusion alteration. Thus, for decades it has been realized that the important strategy to increase survival of septic patients is by optimizing patients' perfusion, both macro- and microcirculation, by adequate initial resuscitation using several resuscitation endpoints. Two of microcirculation resuscitation endpoints, i.e. lactate clearance and $ScvO_2$, that were used in this trial was the widely accepted and studied targets.[8-11,27,28] However, there is scarcity in trial that studied the potential benefit of using combination of both parameters compared to using either parameter. A study by Ali, et al[29] showed that using those combination parameters do not predict mortality in ICU patients. In contrast to our study, this study was not exclusively done in septic patients and use all ICU mortality as the target outcome, not specifically studied early mortality period when perfusion alteration is the most prominent pathophysiology of death.

The subjects' characteristic in the **Table 1** showed no difference on demographic characteristic, comorbidity, location and source of infection between subjects in four groups. There is a tendency of differences in number of organ dysfunction based on SOFA, with increasing number of organ dysfunctions in subjects that did not achieve lactate clearance target. Previous study revealed that number of organ dysfunction and lactate clearance are two predictors of early mortality in severe sepsis and septic shock.[20-24] Thus, as had been planned before, we had adjusted the finding in Cox's proportional hazard regression analysis with number of organ dysfunction.

The Cox's proportional hazard regression analysis showed that there were significant risk differences between subjects achieved both targets with subjects who achieved $ScvO_2$ target only and subjects who did not achieve any target; while there was insignificant risk difference with subjects achieved lactate clearance target only. This finding persist in the multivariate analysis. The result of our study was similar to study by Ali, et al[29] which was done in general critically ill patients. In addition, our sub group analysis further supports the conclusion that achievement of lactate clearance target was superior to $ScvO_2$ target.

Lactate clearance had been extensively studied and shown consistently as significant risk factor of morality in sepsis and septic shock patients, although Surviving Sepsis Campaign 2016 had not recommended a specific nominal target. The committee suggest normalization of lactate in the initial resuscitation of sepsis-induced hypoperfusion.[3] Lactate clearance cut off >10 was initially proposed by Ngunyen, et al[10] based on its ability to predict 60-days mortality of severe sepsis and septic shock patients. This cut-off had also been used in other similar study and revealed consistent result.[8,12] Moreover, in group of patients who achieved lactate clearance target, there were decrease level of biomarkers (including inflammation, coagulation and apoptosis parameters, i.e. IL-6, IL-8, IL-10, IL-1ra, tumor necrosis factor-alpha, intercellular adhesion molecule-1, high mobility group box-1, d-dimer and caspase-3) compared to patients who did not achieve lactate clearance target. Those biomarkers were related to the pathogenesis of multi organ dysfunction and mortality in sepsis.[30]

Thus, the ability of lactate clearance to predict survival of sepsis and septic shock patients is biologically plausible.

The inability in addition of $ScvO_2$ target to lactate clearance target to predict mortality can be elaborated by several limitation of $ScvO_2$ use. Three studies concluded that $ScvO_2$ has poor correlation with mixed venous oxygen saturation (SvO_2), which was the actual parameter that physiologically describes balance between oxygen delivery and consumption. Moreover, $ScvO_2$ reflects mixture of O_2 concentration from various organs. Low O_2 concentration from certain organs can be masked by high O_2 concentration from another organs. Thus, $ScvO_2$ cannot reflect regional perfusion condition, including cerebral perfusion.[31-35] However, our study showed lower mortality risk in group which achieved $ScvO_2$ target only compared to group which did not achieve any targets, reflecting the role of $ScvO_2$ as an endpoint in resuscitations. This finding is in accordance with recommendation of Surviving Sepsis Campaign about the 6 hours of sepsis bundles that did not suggest routine measurement of $ScvO_2$, but as an option method for reassessment of volume status in persistent hypotension after initial fluid administration or if initial lactate was >4 mmol/L.[16] The superiority of lactate clearance to $ScvO_2$ in predicting early mortality can figure the limitation of $ScvO_2$ as one only indicator of oxygen delivery and consumption versus lactate clearance which is a biological reflection of general oxygen homeostasis of the host and adequacy of resuscitation process.[36]

Our study was a retrospective cohort study, with the limitations of retrospective cohort study. However, study was done from Intensive Care Unit medical records with detail history notes on patients clinical and laboratory progress that suffices to extract data needed for this study. Another limitation of our study was the unbalanced number of subjects in the four groups despite the total subjects meet the minimum sample size required for statistical analysis. However, the accordance of this study to the results of previous other sepsis studies with different setting and objectives, will not cause bias on findings of this study.

CONCLUSION

In patients with sepsis and septic shock, achievement of lactate clearance and $ScvO_2$ targets was associated with similar early mortality risk compared lactate clearance target only. However, it was associated with lower early mortality risk compared with $ScvO_2$ target only. In cases of limited health care resources, we thus suggest the priority of choosing lactate clearance as a microcirculation resuscitation endpoint.

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REFERENCES

1. Singer M, Deutschman CS, Seymour CW, et al. The Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016;315:801-10.
2. Seymour CW, Liu VX, Iwashyna TJ, et al. Assessment of clinical criteria for sepsis: for the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016;315:762-74.
3. Rhodes A, Evans LE, Alhazzani W, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. Crit Care Med. 2017;45:486-552.
4. Hollenberg SM. General hemodynamic support. In: Vincent JL, Carlet J, Opal SM, editors. The sepsis text. Massachusetts: Kluwer Academic Publishers; 2002. p. 375-87.
5. Jones AE, Puskarich MA, Sepsis-induced tissue hypoperfusion. Crit Care Clin. 2009;25:769-79.
6. Otero RM, Ngunyen HB, Huang DT, et al. Early goal-directed therapy in severe sepsis and septic shock revisited: concepts, controversies, and contemporary findings. Chest. 2006;130;1579-95.
7. Trzeciak S, Cinel I, Dellinger RP, et al. Resuscitating the microcirculation in sepsis: the central role of nitric oxide, emerging concepts for novel therapies, and challenges for clinical trials. Acad Emerg Med. 2008;15:399–413.

8. Arnold RC, Shapiro NI, Jones AE, et al. Multicenter study of early lactate clearance as a determinant of survival in patients with presumed sepsis. Shock. 2009;32:35-9.
9. Jones AE, Shapiro NI, Trzeciak S, Arnold RC, Claremont HA, Kline JA. Lactate clearance vs central venous oxygen saturation as goals of early sepsis therapy: a randomized clinical trial. JAMA. 2010;303:739-46.
10. Nguyen HB, Rivers EP, Knoblich BP, et al. Early lactate clearance is associated with improved outcome in severe sepsis and septic shock. Crit Care Med. 2004;32:1637-42.
11. Shapiro NI, Howell MD, Talmor D, et al. Serum lactate as a predictor of mortality in emergency department patients with infection. Ann Emerg Med. 2005;45:524-8.
12. Trzeciak S, Dellinger RP, Chansky ME, et al. Serum lactate as a predictor of mortality in patients with infection. Intensive Care Med. 2007;33:970-7.
13. Mouncey PR, Osborn TM, Power GS, et al. Trial of early, gol-directed resuscitation for septic shock. N Engl J Med. 2015;372:1301-11.
14. ProCESS Investigators, Yealy DM, Kellum JA, Huang DT, et al. A randomized trial of protocol-based care for early septic shock. N Engl J Med. 2014;370:1683-93.
15. The ARISE investigators and the ANZICS clinical trials group. Goal-directed resuscitation for patients with early septic shock. N Engl J Med. 2014;371:1496-506.
16. Surviving sepsis campaign. Updated bundles in response to new evidence. 2015.
17. Macias WL, Nelson DR. Severe protein C deficiency predicts early death in severe sepsis. Crit Care Med. 2004;32:S223-8.
18. Mikkelsen ME, Gaieski DF, Goyal M, et al. Factors associated with nonadherence to early goal-directed therapy in the ED. Chest. 2010;138:551-8.
19. Phua J, Koh Y, Du B, et al. Management of severe sepsis in patients admitted to asian intensive care units: prospective cohort study. BMJ. 2011;342:d3245.
20. Sinto R, Suwarto S, Sedono R, Harimurti K, Sejati A. Endpoint resuscitation-based prediction model for early mortality of severe sepsis and septic shock. Crit Care. 2014;18(Suppl 1):P62.
21. Moreno R, Vincent JL, Matos R, et al. The use of maximum SOFA score to quantify organ dysfunction/ failure in intensive care: results of a prospective, multicentre study. Int Care Med. 1999;25:686–96.
22. Ssekitoleko R, Pinkerton R, Muhindo R, Bhagani S, Moore CC. Aggregate evaluable organ dysfunction predicts in-hospital mortality from sepsis in uganda. Am J Trop Med Hyg. 2011;85:697–702.
23. Blanco J, Muriel-Bombín A, Sagredo V, et al. Incidence, organ dysfunction and mortality in severe sepsis: a spanish multicentre study. Crit Care. 2008;12:R158.
24. Esper AM, Martin GS. Extending international sepsis epidemiology: the impact of organ dysfunction. Crit Care. 2009;13:120.
25. Osuchowski MF, Welch K, Yang H, Siddiqui J, Remick DG. Chronic sepsis mortality characterized by an individualized inflammatory response. J Immunol. 2007;179:623-30.
26. Xiao H, Siddiqui J, Remick DG. Mechanisms of mortality in early and late sepsis. Infect Immun. 2006;74:5227-35.
27. Rivers EP, Katranji M, Jaehne KA, et al. Early interventions in severe sepsis and septic shock: a review of the evidence one decade later. Minerva Anestesiol. 2012;78:712-24.
28. Rivers EP, McIntyre L, Morro DC, Rivers KK. Early and innovative interventions for severe sepsis and septic shock: taking advantage of a window of opportunity. CMAJ. 2005;173:1054-65.
29. Ali A, Gearay S, Bennett D, Terblanche M. Lactate and $Scv0_2$ combinations do not predict mortality in ICU patients. Crit Care. 2010;12(Suppl 1):P158.
30. Ngunyen HB, Kuan WS, Batech M, et al. Outcome effectiveness of the severe sepsis resuscitation bundle with addition of lactate clearance as a bundle item: a multi-national evaluation. Crit Care. 2011;15:R229.
31. Beest PA, Hofstra JJ, Schultz MJ, Boerma EC, Spronk PE, Kuiper MA. The incidence of low venous oxygen saturation on admission the the intensive care unit: a multi-center observational study in the Netherlands. Crit Care. 2008;12:R33.
32. Ho KM, Harding R, Chamberlain J, Bulsara M. A comparison of central and mixed venous oxygen saturation in circulatory failure. J Cardiothorac Vasc Anesth. 2010;24:434–9.
33. Kopterides P, Bonovas S, Mavrou I, Kostadima E, Zakynthinos E, Armaganidis A. Venous oxygen saturation and lactate gradient from superior vena cava to pulmonary artery in patients with septic shock. Shock. 2009;31:561-7.
34. Nagdyman N, Fleck T, Barth S, et al. Relation of cerebral tissue oxygenation index to central venous oxygen saturation in children. Int Care Med. 2004;30:468-71.
35. Varpula M, Karlsson S, Ruokonen E, Pettila V. Mixed venous oxygen saturation cannot be estimated by central venous oxygen saturation in septic shock. Int Care Med. 2006;32:1336–43.
36. Jones AE, Jackson MS. Point: should lactate clearance be substituted for central venous oxygen saturation as goals of early severe sepsis and septic shock therapy? yes. Chest. 2011:1406-7.